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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,069	04/04/2001	Yaakov Naparstek	56040-B/JPW/GJG/CSN	3884

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
03/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/826,069	NAPARSTEK, YAAKOV	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/19/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 1/19/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's remarks and IDS filed 1/19/09 have been entered.

2. Claims 8-13 are being acted upon.

3. As set forth previously, the priority date of the instant application is its filing date, 4/04/2001.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 8-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gaubitz et al. (1999) in view of U.S. Patent No. 6,228,363 and Madaio et al. (1996).

As set forth previously, Gaubitz, M., et al. teaches a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies. The reference further teaches that dsDNA-Ab play a "pivotal" role in the pathogenesis of SLE and that their removal proved useful for the treatment of the disease (see particularly Introduction and Discussion).

The reference teaching differs from the claimed invention only in that it does not teach a method employing a column comprising the R38 peptide nor the use of a Sepharose™ column.

The '363 patent teaches that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies (see particularly column 3, lines 13-19).

Madaio et al. teaches that dsDNA-Ab from lupus patients also recognize laminin (see particularly Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies, as taught by Gaubitz et al., employing the R38 peptide of the '363 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to employ the R38 peptide on an immunoadsorption column given the teachings of Madaio et al. that dsDNA-Ab from lupus patients also recognize laminin and the '363 patent that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies. Note that Claim 8 is included in the rejection because various types of immunoadsorber matrices (including Sepharose™) for column chromatography were well-known in the art at the time of the invention. The choice of any particular immunoadsorber matrix would have comprised only routine optimization of the claimed method and would have been well within the purview of one of ordinary skill in the art at the time of the invention. Note that new claim 10 does not recite any new limitations because all ligands are coupled to Sepharose™ in some sort of "coupling buffer" (an ordinarily skilled artisan would know that Sepharose™ could not used in a dry form for column chromatography because column chromatography employs the flow of liquid through the column).

As stated in the rejection, the extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies was known in the art. Substituting a ligand known to bind said pathogenic antibodies for the ligand of the primary reference would have been expected function for the binding and removal of said pathogenic antibodies from the plasma.

Applicant argues unexpected results and further argues unexpected results need not be disclosed in the specification.

It is well established that the assertion of unexpected properties in the course of prosecution is not as persuasive as when said results are disclosed in the specification. As set forth in *In re Davies and Hopkins* 177 USPQ 381 (CCPA 1973), the court stated that evidence alleging unexpected properties need not be considered after filing because it properly belonged in the specification as filed:

"There is no specific statutory requirement that compels applicant to disclose all properties of chemical compounds or compositions in his application; insofar as statute is concerned, only disclosure requirements are in first paragraph of 35 U.S.C. 112; however, public will derive the most benefit from a patent when it discloses on its face those properties or utilitarian advantages which were ultimately persuasive on question of nonobviousness".

While a case of *prima facie* obviousness can be rebutted by a showing of unexpected results, said results properly belong in the specification. Much the same as in this case, the court stated:

"Apparently it was only in the face of the rejections based on this art that appellants were moved to attempt to distinguish the properties obtained using the copolymer as a toughening agent versus using a homopolymer of butadiene".

The court concluded:

"Nevertheless, the public will derive the most benefit from a patent when it discloses on its face those properties or utilitarian advantages which were ultimately persuasive on the question of nonobviousness. However, when, as here,

an applicant has satisfied the requirements of § 112, we would be reluctant to require him to disclose more unless it could be done without prejudice to him. But if the applicant can be required to include the properties in his specification without prejudice to him, a compromise is reached upon which the evidentiary ruling can be based".

Further, a proper showing of unexpected results would also include both statistical evidence and a comparison to the most closely related prior art, neither of which are provided here.

Applicant cites the 9/17/07 1.132 declaration of Inventor Naparstek.

The Inventor states in paragraph 8 that the claimed method has been performed on two patients and that in a single patient, "As shown in Figure 12, the level of anti-VRT (R38) antibodies decreased after the Luposorb™ apheresis and returned to the original levels after more than 5 weeks." In paragraph 10 the Inventor states, "As stated in paragraph 8 above, the continuing decline in antibody levels is an unusual and unexpected result, one that could not have been predicted from the disclosure of any of the references cited, nor any reference known to me".

First note that the Inventor's statements are unclear and confusing in that paragraph 10 refers to a conclusion that is not drawn in paragraph 8. Regardless, a review of the data of Figure 12 reveals that it is not statistically significant and thus is of questionable probative value. Further, there is no comparison to the closest prior art and no showing that the decline in antibody levels is actually unexpected. Finally note that it appears that a rebound effect is demonstrated wherein antibody levels are actually higher at day 58 than they were pretreatment. If said data were to be found to be persuasive said data might necessitate a rejection for lack of enablement.

Applicant cites the additional 1.132 declaration of Inventor Naparstek of 12/10/07.

The Inventor cites two references, Gokhale et al. and Grainger et al., to argue that an antibody rebound effect often follows plasmapheresis. The Inventor further argues that the rebound effect was not seen with the method of the instant claims.

As set forth in Grainger et al. the antibody rebound effect after the removal of all antibodies from a subject's plasma has been observed previously. Thus, sound scientific reasoning and common sense would dictate that improved plasmapheresis methods would seek to avoid this effect. Clearly, the concept of removing only pathogenic antibodies from a subject's plasma comprises the next logical step and does not require great insight. Thus, the claimed method would have been obvious to the ordinarily skilled artisan at the time of the invention.

The value of post-filing results submitted only in an attempt to overcome an obviousness rejection has been discussed above. Further regarding the instant results, however, it is unclear whether or not the antibody rebound effect is actually avoided with the method of the instant claims. Note that the effect was not seen in the patient of the Inventor's 9/17/07 declaration until day 58 post plasmapheresis. In the data of the instant declaration the post treatment antibody levels are disclosed only after "one month". Accordingly, it is unclear what the antibody levels might rise to after two months or longer.

Applicant's arguments, filed 6/29/08, have been fully considered but they are not persuasive. Applicant discusses the Gaubitz et al. reference and argues that it differs from the claimed invention in that it does not teach the removal from plasma of lupus-specific antibodies.

Applicant's argument is noted. It is the combination of the three references that results in the obviousness of the method of the instant claims. Also note that there is nothing novel regarding the removal of specific antibodies from a solution employing a column comprising an antibody's antigen. Said removal is referred to as immunopurification and has been a routine laboratory practice for decades.

Applicant argues that "the statement that, "removal of pathogenic antibodies was known" is not exactly correct".

The statement stands and it is correct. The fact that Applicant prefers a statement of his own choosing has no bearing on the factuality of the Examiner's position.

Applicant argues that, "there is no guarantee" that anti-R38 antibodies that bind R-38 on an ELISA plate would bind R38 on a column.

There would be every expectation of success and Applicant has offered no evidence that this routine practice would not work. Applicant's allegations of unpredictability in a field that has produced highly predictable results for decades are not persuasive.

Applicant again argues unpredictable results citing additional results provided by the Inventor in a new 1.132. declaration, and states that a comparison to the closest prior art cannot be done.

Applicant's new results are noted, but given Applicant's incredible statement it is clear then that Applicant cannot demonstrate unpredictable results. Accordingly, the results cannot be considered to be sufficient to overcome the finding of obviousness. An attorney's mere statement that results are unexpected is not persuasive.

Applicant asks the Examiner to explain Applicant's results.

Applicant is advised that it is not the Examiner's burden to explain Applicant's results.

Applicant rejects the holdings in *Davies and Hopkins* and cites *Knoll v. Teva*.

Applicant may reject the court's holdings but they stand never the less. Regarding *Knoll v. Teva,* the fact pattern in the case is quite different from that in the instant case. First, the application *did* cite surprising results (which is not the case here). Second, the issue was technical in nature, i.e., whether or not a summary judgment by a district court was proper (it was not). Third, the court ruled regarding the new submission of unexpected results in "response to a litigation attack", not in the prosecution of a patent application. Finally, the court simply reversed and remanded the case to the district court for further review.

Regarding a more recent case, in one of the few obviousness cases post *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the court held in *Leapfrog*

Enterprises Inc. v. Fisher-Price Inc., 82 USPQ2d 1687 (Fed. Cir. 2007) that even with a showing of "substantial" secondary considerations an invention can still be held to be obvious. Thus, in the instant case the combination of routine methods, that have been repeatedly and predictably employed for decades, is still obvious even in light of Applicant's asserted secondary unexpected results that Applicant states cannot be compared to the closest prior art and shown to actually be unexpected.

Applicant's arguments, filed 1/19/09, have been fully considered but they are not persuasive. Applicant again argues that evidence of unexpected results need not be appear in the specification.

The issue has been addressed previously.

Applicant submits Hershko and Naparstek (2005) in support of the argument that in view of the prior art the method of the instant claims had no reasonable expectation of success.

The introduction of the reference teaches, "Until two decades ago, therapeutic plasma exchange was the only procedure used for antibody removal from the plasma", followed by a review of newer methods designed to remove only specific pathogenic antibodies. This teaching demonstrates that the removal of antibodies from the blood for the treatment of certain diseases is a very well-known concept. The reference continues by discussing the methods as they are used in the treatment of three diseases, MG, DCM, and SLE.

Applicant argues that treatment of MG by the removal of specific antibodies was unsuccessful.

Applicant's position is acknowledged. However, a review of the reference reveals that the apparent failure of the method in the context of MG was due to the low affinity of a single peptide for a single antibody. Contrast that with the successes in treating SLE. At page 637 the reference teaches that in one method anti-dsDNA complexes were eliminated and inflammation was ameliorated. Note that anti-dsDNA antibodies are the ligand for the R38 peptides employed in the method of the instant claims. Also see pages 640-641 wherein the authors teach that SLE can be effectively treated through the removal of anti-dsDNA antibodies, e.g., the quality of life of SLE patients improved due to a reduction in anti-dsDNA antibodies after being administered LJP394. Indeed, the reference supports the Examiner's position of obviousness in stating, "Peptide-bound

columns allow specific removal of the pathogenic antibodies, implying that extracorporeal specific immunoadsorption on the laminin-epitope columns may serve as a new therapeutic alternative for SLE".

The position of the authors seems to be one of guarded optimism with the major concern being that pathogenic autoantibodies need to be identified before the method can be used. But fortunately, with SLE, pathogenic autoantibodies have been identified. The authors teach that it is the anti-dsDNA antibodies that are involved with renal disease that are pathogenic in the disease. While direct evidence might be lacking, the fact that the method of reducing levels of anti-dsDNA antibodies has been demonstrated to treat the disease is enough to render the method of the instant claims obvious in view of the prior art.

Applicant concludes by raising a number of possible issues that might render the claimed method ineffective. But note that none of these issues have been seen in the instant case. The r38 peptide *does* bind anti-dsDNA and countless peptides *have* been attached to columns for the purification of antibodies, indeed, the method is known as antibody affinity purification and it has been routine for decades. And regarding the final issue of plasma flow rate, the Hershko and Naparstek reference describes at least one type of column (Immunosorba) with a "nearly unlimited" adsorption capacity thus, even this remote issue is really a non-issue.

6. No claim is allowed.

7. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this

action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

9. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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